INITIAL SCREENING OF INCOMING PAPERS CHECKLIST

Reviewer: JChase Date: 8-25-03

APPLICATION NO. 09/707905

1. PETITION TYPE CODE

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2. LIST PAPERS FILED WITH PETITIONS

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____	Brief (3)	____	Drawings	____	Oath/Decl. & POA
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____	Declaration R132	____	Ext Time (___)	____	Statement 3.73(b)

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3. Is paper a petition to withdraw holding of abandonment: ____yes____no
If so, send paper and/or file to appropriate location ***(Note: remove any flag set first)***:

a. Nonreceipt of action from TC or assertion that reply was timely filed:
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b. Nonreceipt of Missing Parts Notice or assertion that reply was timely filed:
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c: Assertion of timely payment of issue fee and/or submission of drawings:
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5. Is petition accompanied by assignment papers, fee address, or other paper which needs to be sent to another location? ____ yes ____ no If so, make copy of assignment papers, fee address, or other paper; mail original to proper location and place copy in file with an indication that the original paper(s) has been forwarded to the appropriate location (Assignment Branch; Maintenance Fee Division, etc.)

8-18-03

3DAC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Ramnarayan *et al.*
Serial No.: 09/709,905
Confirmation No.: 3606; Cust. No. 24961
Filed: November 10, 2000

For: *USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG DESIGN AND CLINICAL APPLICATIONS*

Art Unit: 1631
Examiner: Brusca, J.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"Express Mail" Mailing Label Number EV 335463259 US
Date of Deposit August 14, 2003

I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 C.F.R. §1.10 on the date indicated above and addressed to:
Mail Stop Petition
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

Michael Lough

TRANSMITTAL OF PETITION UNDER 37 C.F.R. §1.181

Mail Stop Petition
Commissioner for Patents
Alexandria, VA 22313

Dear Sir:

Transmitted herewith are a Petition under 37 C.F.R. §1.181 (regarding the propriety of a determination that a Response is not fully responsive to a previous Office Action) responsive to the Office Communication mailed July 2, 2003; a check in the amount of $130 for the Petition fee; and a return postcard. If a Petition for extension of time is needed, this paper is to be considered such Petition.

☒ The Commissioner is hereby authorized to charge the deficiency in the above check and any fee that may be due in connection with this and the attached papers, or with this application during its entire pendency to or to credit any overpayment to Deposit Account No. 50-1213. A duplicate of this sheet is enclosed.

Respectfully submitted,
HELLER EHRMAN WHITE & MCAULIFFE LLP

By: _____
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Mail Stop Petition
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

Michael Lough

PETITION UNDER 37 C.F.R. §1.181 REGARDING PROPRIETY OF A DETERMINATION THAT A RESPONSE TO A PREVIOUS OFFICE ACTION IS NOT FULLY RESPONSIVE

Mail Stop Petition
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

Applicant hereby petitions under 37 C.F.R. §1.181 the determination in an Office Communication, mailed on July 2, 2003, that Applicant's response to the previous Office Action is not fully responsive as adding subject matter allegedly withdrawn from consideration. A fee for this Petition is attached hereto. Any fees that may be due in connection with this paper or with this application may be charged to deposit Account No. Deposit Account No. 50-1213.

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Statement of Facts

Office Action dated August 7, 2002

A written restriction requirement was set forth in an Office Action, mailed August 7, 2002. The requirement set forth nine (9) Groups for election. The groups were as follows:

Group I: Claims 1-25, 45-50, 66, 67 and 87-90, directed to a method of designing drug that act on polymorphic proteins;
Group II: Claims 26, 27, 82 and 91, directed to a method of selection of a drug therapy;
Group III: Claims 29, 68-74, 80 and 92, directed to a method of predicting a clinical response;
Group IV: Claim 30, directed to a method of designing therapeutic agents that are active against biological targets that have become drug resistant due to genetic mutations;
Group V: Claims 31 and 93, directed to a method of identifying compensatory mutations in a target protein;
Group VI: Claims 32-44 and 84-86, directed to a method of creating a 3-D structural polymorphism relational database;
Group VII: Claims 51-53, directed to a computer;
Group VIII: Claims 54-65, directed to a database; and
Group IX: Claims 75-79, 81, 83 and 94, directed to a method of predicting resistance.

Applicant elected, without traverse, Group I, claims 1-25, 45-50, 66, 67 and 87-90, directed to a method of designing drugs, for examination on the merits. Claim 1 is as follows:

> 1. A computer-based method of drug design based on genetic polymorphisms, comprising:
>
> obtaining more than one amino acid sequence of target proteins that are the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;
>
> generating 3-dimensional (3-D) protein structural variant models from the sequences; and
>
> based upon the structures of the 3-D models, designing drug candidates, modifying existing drugs, identifying potential drug candidates or identifying modifications of existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants.

Claim 1 is directed to a computer-based method of drug design in which three dimensional (3-D) models of structural variant target proteins that are the product of a gene exhibiting genetic polymorphisms are generated and used for a variety of purposes, including designing drug candidates, modifying existing drugs, identifying potential drug candidates, and identifying modifications of existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants of the target proteins. The claim does not set forth any specific method by which 3-D models of target proteins are generated. Claims 2-25, 45-50, 66, 67, and 87-90 are dependent on claim 1 and further define the structure based drug design, target proteins, selection of model structures, determination of binding interactions, analysis of structure of target proteins to determine common structural features, and storage of structures in a database. The claims are not limited to *ab initio* methods for generating structures of proteins.

Office Action of December 3, 2002

The first Office Action on the merits was mailed on December 3, 2002, rejecting all claims under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most clearly connected, to make and/or use the claimed subject matter because it would require under experimentation to generate 3-D protein structural variant models because *ab initio* methods allegedly do not work.

A response addressing this rejection and all other issues raised, and amending the claims for clarity and adding claims directed to specific embodiments was mailed on June 3, 2003. Therefore, the Response is fully responsive to the prior Office Action.

In particular, to address issues in the Office Action, the claims are amended and added to effect clarity. For example, in the Response dated June

3, 2003, claim 1 is amended as follows (where strikethrough denotes deleted text and underlining denotes added text):

1. (Amended) A computer-based method of drug design based on genetic polymorphisms, comprising:

identifying target proteins that are the product of a gene exhibiting genetic polymorphisms;

obtaining more than one amino acid sequences of the target proteins that are the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

~~generating~~ determining 3-dimensional (3-D) protein structural variant models ~~from the sequences~~ for the target proteins that are the product of a gene exhibiting genetic polymorphisms; and

based upon the structures of the 3-D models of the target proteins that are the product of a gene exhibiting genetic polymorphisms, designing drug candidates, modifying existing drugs, identifying potential drug candidates or identifying modifications of existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants of the target proteins.

In the amendment of claim 1, the phrase "generating 3-dimensional (3-D) protein structural variant models from the sequences" is replaced with the phrase —determining 3-dimensional (3-D) protein structural variant models for the target proteins that are the product of a gene exhibiting genetic polymorphisms— to render it clear that (1) the 3-D structures of the protein structural variant models are determined and (2) the proteins whose structures are determined are the product of a gene exhibiting genetic polymorphisms.

Dependent claims were amended to correct minor grammatical inconsistencies and/or to properly depend from claim 1. New claims 95-127, directed to particular embodiments of claim 1 were added. For example, claims 101-109 are added:

> 101. (New) The method of claim 1, wherein the step of determining 3-D protein structural variant models is performed by a method selected from the group consisting of experimental methods, searching protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, *ab initio* methods and combinations thereof.

102. (New) The method of claim 101, wherein the experimental methods include x-ray crystallography and NMR spectroscopy.

103. (New) The method of claim 1, wherein the step of determining 3-D protein structural variant models is performed by a combination of homology modeling and *ab initio* methods.

104. (New) The method of claim 13, wherein the step of determining 3-D protein structural variant models is performed by a method selected from the group consisting of experimental methods, searching protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, *ab initio* methods and combinations thereof.

105. (New) The method of claim 104, wherein the experimental methods include x-ray crystallography and NMR spectroscopy.

106. (New) The method of claim 13, wherein the step of determining 3-D protein structural variant models is performed by a combination of homology modeling and *ab initio* methods.

107. (New) The method of claim 15, wherein the step of determining 3-D protein structural variant models is performed by a method selected from the group consisting of experimental methods, searching protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, *ab initio* methods and combinations thereof.

108. (New) The method of claim 107, wherein the experimental methods include x-ray crystallography and NMR spectroscopy.

109. (New) The method of claim 15, wherein the step of determining 3-D protein structural variant models is performed by a combination of homology modeling and *ab initio* methods.

New claims 101-109 are dependent on claim 1, as amended in the Response dated June 3, 2003, and are directed to a computer-based method of designing drugs, which is the subject matter of the originally elected claims. New claims 101-109 are added to render it clear that a variety of methods, not just *ab initio* methods, can be used to determine 3-D structures of target proteins based upon sequences, just as a variety of methods can be used to determine the 3-D structures of proteins in the original claims. Thus, new claims 101-109 are added for clarity without altering the scope of the originally elected claims. All of the added claims fall within the purview of the elected

subject matter and, thus, do not add subject matter withdrawn from consideration.

Office Communication dated July 2, 2003

In an Office Communication dated July 2, 2003, the claims that were amended and added in the Response dated June 3, 2003, were deemed to be directed to a subject matter that is distinct and independent from the originally elected subject matter. On this basis, the Response dated June 3, 2003, was not considered to be fully responsive. The Examiner alleges that the originally elected subject matter required *ab initio* determination of a 3-D protein from a polypeptide sequence and that because the newly added and amended claims include a variety of methods for determining protein structures from sequences, the newly added and amended claims are directed to subject matter withdrawn from consideration by original presentation. It is this finding that is Petitioned herein.

It is respectfully submitted that the Examiner is incorrect in concluding that the Response dated June 3, 2003, is not fully responsive. The response is fully responsive because (1) all rejections were addressed; (2) the originally elected claims encompass any method for determining 3-D protein structure, not only *ab initio* methods; and (3) the claims that were amended and added in the Response dated June 3, 2003, are drawn to the same subject matter as the originally elected claims. The originally elected claims and the amended claims encompass, but are not solely limited to, methods of designing drugs based on polymorphisms that employ *ab initio* methods. Therefore, it is respectfully submitted that the Examiner's determination that the response dated June 3, 2003, is not responsive is improper.

Analysis

The elected claims encompass any method for generating 3-D protein structures.

The Examiner alleges in the Office Communication dated July 2, 2003, that the originally elected claims require *ab initio* determination of a 3-D protein structure from a polypeptide sequence, and that the amendment filed June 3, 2003, deletes this limitation. Neither the original claims nor the claims that were amended and added in the Response dated June 3, 2003, are limited to *ab initio* methods for generating structures of proteins; none of the original claims included such limitation. As such, the amended and added claims are not adding subject matter that has been withdrawn from consideration and should be examined as part of the elected subject matter.

As noted above, original claim 1 is as follows:

> 1. A computer-based method of drug design based on genetic polymorphisms, comprising:
>
> obtaining more than one amino acid sequence of target proteins that are the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;
>
> generating 3-dimensional (3-D) protein structural variant models from the sequences; and
>
> based upon the structures of the 3-D models, designing drug candidates, modifying existing drugs, identifying potential drug candidates or identifying modifications of existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants.

Original claim 1 clearly does not include a recitation that the protein structures are generated by *ab initio* methods. Claim 1 is a generic claim that encompasses any method for generating 3-D protein structures from sequences that is consistent with the disclosure of the specification.

As stated in the MPEP 904.01,

> The breadth of the claims in the application should always be carefully noted; that is, the examiner should be fully aware of what the claims do not call for, as well as what they do require. During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See *In re Morris*, 127 F.ed 1048, 44 USPQ2d 1023 (Fed. Cir. 1997).

As stated in the MPEP 2111, paragraph 1,

> During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)

Thus, in view of MPEP 904.01 and MPEP 2111, paragraph 1, claim 1 and claims dependent thereon should be given the broadest reasonable interpretation that is consistent with the specification. Although the specification should not be read into the claims, the teachings of the specification should not be ignored if claims are to be given their broadest reasonable interpretation in light of the specification.

It is respectfully submitted that interpreting the originally elected claims as requiring only *ab initio* methods does not provide these claims their broadest reasonable interpretation, and is not consistent with the specification, As discussed in the Response dated June 3, 2003, the specification does not teach that *ab initio* methods are required to generate 3-D structures of proteins as used in the claimed methods. In particular, the specification teaches (see, *e.g.*, pages 25-34) that 3-D protein structures can be generated by a variety of methods, including *ab initio* methods. The specification states (emphasis added):

> **2. Generation of 3-D protein structural variant models**
> *After the amino acid sequences of target proteins are obtained via the means described in section 1, the 3-D structural models of the sequences of native proteins or of the protein structural variants are then*

> *determined.* They can be determined through experimental methods, such as x-ray crystallography and NMR, and from structure databases, such as the Protein Databank (PDB). Moreover, *3-D structural models can be determined by using any of a number of well known techniques* for predicting protein structures from primary sequences (e.g. SYBYL (Tripos Associated, St. Louis, Mo.), *de novo* protein structure design programs (e.g. MODELER (MSI, Inc., San Diego, CA) and MOE (Chemical Computing Group, Montreal Canada) and *ab initio* methods, see, *e.g.*, U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895), homology modeling, and *ab initio* computational analysis. Homology modeling, structure determination based upon x-ray crystallographic structures, and *ab initio* techniques and combinations of these methods are among those preferred herein.

Hence it is clear that the step of generating 3-dimensional (3-D) protein structural variant models from the sequences of the polypeptides is not intended to be limited to *ab initio* methods. The claim does not recite that the 3-D protein structural variant models are determined by *ab initio* methods only, and the supporting disclosure in the specification teaches that this step can be effected by a variety of methods.

Thus, based on the language of the claim and the support illustrated in the specification, claim 1, as originally filed, and claims dependent thereon encompass a variety of methods, including *ab initio* methods, for use in methods as claimed. Therefore, contrary to the Examiner's assertion, the scope of the originally elected claims is generic and does not only encompass *ab initio* methods. Thus, there was no *ab initio* method limitation in the originally elected claims to delete by the amendment dated June 3, 2003.

Furthermore, the claims that were amended and added in the Amendment dated June 3, 2003, do not delete *ab initio* methods as a way of determining 3-D models of target proteins. In fact, these claims recite that a variety of methods can be used to determine 3-D models of target proteins; these include *ab initio* methods. As discussed above, amended claim 1 reads as follows:

1. (Amended) A computer-based method of drug design based on genetic polymorphisms, comprising:

identifying target proteins that are the product of a gene exhibiting genetic polymorphisms;

obtaining more than one amino acid sequences of the target proteins that are the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

determining 3-dimensional (3-D) protein structural variant models for the target proteins that are the product of a gene exhibiting genetic polymorphisms; and

based upon the structures of the 3-D models of the target proteins that are the product of a gene exhibiting genetic polymorphisms, designing drug candidates, modifying existing drugs, identifying potential drug candidates or identifying modifications of existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants of the target proteins.

Thus, amended claim 1 does not delete an *ab initio* step of determining 3-D structural variant models, but clarifies to the language of the claim to render it clear that the variant models are determined from the product of the gene exhibiting genetic polymorphisms. The amended claim is of identical scope to the original claim.

Even *assuming arguendo*, that a step of generating 3-D structures of proteins "from the sequence" requires *ab initio* methods, which it does not, there is nothing in the specification nor the original claims that teaches that this step is limited solely to *ab initio* methods and to no other methods. In fact, the specification teaches that *ab initio* methods can be used in combination with other methods, such as experimental methods and homology modeling, to generate 3-D protein structures (pages 25-34 and the Examples). Therefore, the originally elected claims are not limited solely to *ab initio* methods for generating structures of proteins.

Methods including step of generating protein structures from sequences by any method were not withdrawn from consideration.

As noted above, the subject matter of the originally elected group is a computer-based method of designing drugs based on genetic polymorphisms, in which 3-D models of target proteins are used to design drug candidates, modify

existing drugs, identify potential drug candidates or identify modifications of existing drugs. Claim 1 as amended in the Response dated June 3, 2003, is still directed to the same subject matter of original claim 1. For example, the original and amended claim 1 recite that 3-D models of target proteins are used in the claimed methods. The 3-D models of target proteins are "determined" in claim 1 as amended in the Response dated June 3, 2003, whereas the 3-D models of target proteins are generated from sequences in original claim 1. Thus, the amendment to claim 1 merely clarifies steps in the claim without altering the scope of the claim.

None of the withdrawn claims are directed to methods of computer-based method of designing drugs based on genetic polymorphisms, in which 3-D models of target proteins are determined from polypeptide sequences by methods other than *ab initio* methods. Accordingly, methods that employ any of the variety of methods described in the specification as encompassed by the original claims are not withdrawn from consideration.

Applicant elected group I for examination on the merits; applicant did not elect a method for designing drugs that included a step in which the 3-D models are generated only by *ab initio* methods. The originally elected claims are directed **a method of designing drugs** in which 3-D protein structures are **generated** from sequences by a variety of methods including, but not limited to, *ab initio* methods. The claims that were amended and added in the Response dated June 3, 2003, similarly are directed **a method of designing drugs** in which 3-D protein structures are **determined** by a variety of methods including, but not limited to, *ab initio* methods. Therefore, contrary to the Examiner's assertion, the Amendment dated June 3, 2003, is directed to the originally elected subject matter, and is thus fully responsive.

CONCLUSION

In view of the above, Applicant petitions for withdrawal of the determination that Applicant's response to the previous Office Action is not fully

responsive as adding subject matter allegedly withdrawn from consideration and petitions for entry of the Response dated June 3, 2003. It is respectfully submitted that based on the language of the claims and the support in the specification, the originally elected claims are not limited to *ab initio* methods for generation of 3-D structures of proteins.

* * *

Respectfully submitted,
HELLER EHRMAN WHITE & MCAULIFFE LLP

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